

Application no.: 09/700,270

Docket no.: SGL-2009-US

REMARKS

In the complete listing of claims provided herein, claims 1 and 4 are amended, claims 5-8 and 12-14 are cancelled and claims 17-29 are new. Basis for the new claims and the claim amendments are in the specification throughout, for example on page 5, line 23 to page 6, line 13 and in the Examples section spanning pages 9-12, and therefore no prohibited new matter has been added. The claims were rejected for alleged lack of enablement, alleged indefiniteness and alleged anticipation. Applicants respectfully submit these rejections are inapplicable to the amended claims, as shown hereafter.

Rejections for Alleged Lack of Enablement

The Office rejected claims 1-7 and 12-16 for alleged lack of enablement under 35 U.S.C. §112, first paragraph. Claims 1 and 4 are the sole independent claims pending, are amended herein for the purpose of expediting prosecution, and the amendments are not an admission that broader subject matter is unpatentable. Claims 1 and 4 are amended to clarify a risk polymorphism for hypertension is a four base-pair insertion located between positions -891 and -575 5' to the transcription start site of the iNOS gene. The specification fully enables these independent claims and their dependent claims.

The Examples section of the specification describes a study demonstrating that a four base-pair insertion located in the region defined by the claims is associated significantly with hypertension. A p-value of 0.016 showed there was a statistically significant association of the four base-pair insertion with risk of hypertension with a statistically significant p-value of 0.016 in a significant number of hypertensive and normotensive subjects (see Table 2, page 12). This section of the specification teaches subject selection criteria, methodology for obtaining nucleic acid samples from subjects, methodology for amplifying and analyzing genotypes of the isolated nucleic acids, and methods for determining whether there is an association between a particular polymorphism and hypertension (e.g., Examples section, pages 9-12). Thus, the specification provides a working example for determining the presence or absence of a hypertension-associated four base-pair insertion in the region specified by the claims. This working example therefore provides clear guidance to the person of ordinary skill in the art for carrying out methods for diagnosing hypertension or predisposition thereto.

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Any other four base-pair insertions in the region specified by the claims can be identified by a person of ordinary skill in the art by routine experimentation. Given the 316 base pairs in the claimed region is defined and relatively small, the person of ordinary skill in the art could identify any four-base pair insertion by routinely conducting known genotyping procedures in additional hypertensive and normotensive subjects. Any nucleic acids with a different size or molecular weight than detected in the specification, for example, could be sequenced to determine whether the modification is a four-base pair insert. With the specification's guidance that the region defined by the claims is associated with hypertension, the person of ordinary skill in the art could conduct a refined search of additional four base-pair insertions by routine experimentation. This experimentation would be routine especially in view of the high level of skill in the art in the genomics field. Because the Court of Appeals for the Federal Circuit has deemed a large quantity of experimentation is acceptable when it is routine, (e.g., *In re Wands*, 8 USPQ.2d 1400, 1404 (Fed. Cir. 1988)), the full breadth of the claimed methods can be conducted without undue experimentation.

Because the specification provides working examples and specific guidance for conducting the claimed methods, and because any experimentation for carrying out the full scope of the claimed methods is not undue, the claimed methods are in accord with the enablement requirements articulated in *In re Wands* and *Ex Parte Foreman*.

In view of these features of the claimed methods and the teachings in the specification, the Applicants do not understand certain statements in the Office action. For example, the Office states on page 4 "the claims can encompass any genotype, disease associated or not, that can be found in the iNOS gene." This statement is not understood as the claimed methods are directed to diagnosing hypertension or a predisposition thereto by determining whether a risk polymorphism is present. Thus, the claim is directed to detecting the presence or absence of a polymorphism associated with hypertension because it is a "risk" polymorphism. The Office also states the specification identifies a four base-pair insertion "that may be associated with hypertension" (page 4, emphasis added), and cites Wacholder *et al.* for the assertion that studies with thousands of participants have more statistical power than studies with a smaller number of participants (page 5). These positions also are not understood. Studies in the specification were conducted with a statistically significant number of subjects and risk of hypertension was determined with statistical significance (note the p-value referenced above). While larger groups of subjects may provide

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additional statistical power in such studies, groups of the size studied in the specification can provide statistically significant disease associations and thereby support the claimed methods.

Accordingly, Applicants respectfully request that the Office withdraw the rejection for alleged lack of enablement under 35 U.S.C. § 112, first paragraph, for these reasons.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office rejected claims 1-6 and 12-16 for alleged indefiniteness under 35 U.S.C. § 112, second paragraph. Applicants respectfully submit the amended claims are clear and definite and that the rejection is inapplicable. Claims 1 and 4 have been amended to recite a definite step for diagnosing hypertension or predisposition thereof, and therefore the goal of the preamble is achieved. Claim 4 has been amended so that it now is independent, thereby removing any issues concerning its dependence upon claim 1. Claims 5 and 12-16 are cancelled. The amendments to claims 1 and 4 and the cancellation of claims therefore render moot the rejection under 35 U.S.C. § 112, second paragraph, and Applicants request withdrawal of the rejection.

Rejections for Alleged Anticipation

The Office rejected claims 1, 3, 5, 6, 12 and 14 for alleged anticipation under 35 U.S.C. § 102(a) in view of WO97/38130 (hereafter "Xu"). The Office also rejected claims 1-2, 5 and 12-13 for alleged anticipation under 35 U.S.C. § 102(a) in view of Bellamy *et al.*, *Clin. Genet.* 52: 192-193 (1997) (hereafter "Bellamy").

The pending claims are directed to methods for diagnosing hypertension or predisposition thereof based upon a tetranucleotide repeat in a specific region of the iNOS promoter. In contrast, Xu discusses a pentanucleotide repeat, not a tetranucleotide repeat, and the repeat characterized is not located in the -891 and -575 region as claimed. Xu also does not demonstrate the pentanucleotide repeat is associated with hypertension.

Bellamy similarly fails to show the polymorphic variant characterized is associated with hypertension. Thus, the presently claimed methods are directed to a method of use not mentioned or addressed in Bellamy.

Accordingly, Applicants respectfully request the Office withdraw the rejections of the amended claims under 35 U.S.C. § 102(a).

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CONCLUSIONS

Applicants respectfully submit the claims pending herein are in condition for allowance, and they solicit an early notice to such effect. The Examiner is encouraged to telephone the undersigned at (858) 623-9470 to promptly resolve any issues or questions that may remain.

In the unlikely event the transmittal letter is separated from this document and the Office determines that an extension and/or other relief is required, Applicants petition for any required relief, including extensions of time, and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 503473**.

Respectfully submitted,

Dated: February 28, 2006By: 

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